

### **REMARKS**

In view of the following remarks, the Examiner is requested to allow Claims 1-3-7, 9-11, 14-16 and 28-37, the only claims pending and under examination in this application, after entry of the above amendments.

Claims 1 and 37 have been amended for clarity.

No new matter is added.

### ***Claim Objections***

The Examiner has objected to the claims because of an informality in Claim 1 and because of misnumbered claims. In view of the currently amended Claim 1 and the numbering correction made by the Examiner, the objections may be withdrawn.

### ***Rejections - 35 USC § 112***

Claims 30-33 have been rejected under 35 U.S.C. 112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. The Applicants traverse this rejection.

The test for definiteness under 35 U.S.C. § 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576; 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986).

In making this rejection, the Examiner asserts that the claims are indefinite because the claims do not define a relationship providing the angle. The Applicants submit that the relationship providing the angle is clearly defined by the two planes recited in the claims: the "plane of the flow cell" and "the horizontal plane of the environment". In addition, the first paragraph on page 30 of the specification also lays out, in an embodiment, the context in which the two planes may define the angle.

As such, in view of the plain language of Claims 30-33 and of the specification, the Applicants submit that there is no ambiguity as to how the angles are defined and one of skilled in the art would understand what is claimed in Claims 30-33. Withdrawal of this rejection is thus respectfully requested.

***Rejections - 35 USC § 103 Bass '180 and Anderson***

Claims 1, 3-4, 28, 34-37 are rejected under 35 U.S.C. 103(a) as being obvious over Bass et al. (USPN 6,410,180) in view of Anderson et al. (USPN 5,186,824). The Applicants traverse this rejection.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. See, e.g., *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, e.g., *KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*. Further, the Supreme Court in *KSR* also stated that that “a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.” *KSR* at 1740. As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

The rejected claims are drawn to a method for synthesizing an addressable array of at least two different polymeric ligands on a substrate. The Applicants submit that Bass '180 in view of Anderson would not lead one of skilled in the art to combine the elements in the manner suggested by the Examiner. For example, the Applicants contend that one of skilled in the art would have no reason to arrive at “displacing a previous liquid of said plurality with an immediately subsequent liquid,” as required by step (c) of Claim 1, without the hindsight provided by the Applicants.

In making this rejection, the Examiner asserts, *inter alia*, that since Anderson's method aims to overcome problems of incompatible or wasted reagents, one of skilled in the art would have been motivated “to apply fluid displacement of Anderson to polymer synthesis of Bass” (page 6 of Final Office Action dated 8/12/08). However, as explained in more detail below, just because Anderson's method allegedly overcomes the problems of incompatible reagents, one of skilled in the art still would have no reason to combine the elements in the manner suggested by the Examiner.

The teaching of Bass '180 relates to a method of pulse jetting reagents onto a substrate and exposing the substrate to certain fluids in a flood station (columns 7-9). However, Bass is completely silent on "displacing a previous liquid [...] with an immediately subsequent liquid," as required by the rejected claims. The Examiner then cites Anderson to remedy Bass's deficiency.

Briefly, Anderson teaches a rotor container with an inlet and outlet to introduce fluids of different density during rotation. The rotor can be used as batch reactor to synthesize oligonucleotides on controlled-pore glass beads (CPG) suspended by the fluids in the rotating rotor. As apparently clear from their methods, the methods of Bass and Anderson are for very different purposes, the former directed to pulse jetting, in which different polynucleotides are synthesized at different locations on an addressable substrate, and the latter directed to a batch synthesis reaction. As such, there is no reason for one of skilled in the art to combine the two references.

Even if the references are combined in an attempt to read onto the rejected claims as suggested by the Examiner, the proposed modification would either change the principle of operation of the methods taught by the references or render them inoperable. Under current law, such logic cannot be used to establish a *prima facie* case of obviousness.

It is well established that a reference cannot render an invention obvious

if the proposed modification or combination of the prior art would  
change the principle of operation of the prior art invention being  
modified...<sup>1</sup>

or

if proposed modification would render the prior art invention being  
modified unsatisfactory for its intended purpose.<sup>2</sup>

In Fig. 1 and 2A-2D of Anderson, solid phase reactions performed on solid support such as CPG are retained in suspension inside Anderson's rotor during fluid displacement. The proposed modification by the Examiner would result in an

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<sup>1</sup> *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); MPEP 2143.01 VI

<sup>2</sup> *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP 2143.01 V

embodiment where the substrate of the addressable array may be damaged while experiencing centrifugal force inside Anderson's rotor. Since a glass bead is not an addressable array nor can Bass's substrate exist in suspension, it would render either Bass's method or Anderson's method inoperable.

This combination would also render Bass's method inoperable for the following reason. As described in the summary of invention and throughout the specification in Bass, reagents are jetted in a pre-determined pattern onto a substrate. Such contact printing to specific addresses on an array substrate would be inoperable if the substrate were to be enclosed and suspended in Anderson's rotor.

Furthermore, the proposed modification would change the principle of operation of the cited references. A mounted substrate in Anderson's rotor would not contain the element of suspended solid-phase in a rotating chamber taught by Anderson. As for Bass, Bass's array would not comprise of pulse jetting since nothing in Anderson's rotor would accommodate such contact printing onto an array. A *prima facie* case of obviousness cannot be established by completely eliminating the principles of operation of Bass or Anderson.

Moreover, the Applicants contend that a careful consideration of the field of array synthesis reveals that the much of the teaching around the priority date of the instant application comprises drying steps in between wash steps and is completely devoid of the element of "displacing a previous liquid of said plurality with an immediately subsequent liquid." Certain patents are discussed briefly below to illustrate the prevalent practice of air drying in the field of array synthesis and the lack of teaching of "displacing a previous liquid [...] with an immediately subsequent liquid."

One such reference is Glazer et al. (USPN 6,824,866), in which the performance of an array substrate was tested by synthesizing fluorescein phosphoramidite onto the substrate. In column 22, lines 43-45 of Glazer, the substrates are "deprotected [...] and blown dry with dry nitrogen."

Another reference, Gamble (USPN 5,981,733) teaches jetting deprotecting agents onto the array substrate and drying the substrate after a washing step with compressed gas (column 13, lines 6-15).

In Blanchard et al. (USPN 6,028,189) and Blanchard et al. (USPN 6,419,883), the methods taught in both references require “drying in a stream of dry nitrogen” between fluid exposures in columns 12 and 38, respectively.

Schermer et al. (USPN 6,485,918) teaches an apparatus for array synthesis that performs “automatic washing and drying.” The method taught by Schermer also involves jetting wash solutions and vacuum or gas-stream drying (column 8, lines 47-59).

In view of the above-cited patents, the prevalent teachings in the art of array synthesis employ air drying in between steps of array synthesis and are completely silent on “displacing a previous liquid [...] with an immediately subsequent liquid.” As such, without the hindsight provided by the Applicants’ application, one of skilled in the art would not have any reason to combine Bass and Anderson teachings in the manner suggested by the Examiner to arrive at the rejected claims.

In view of the foregoing discussion, the Applicants submit that the rejected claims are not obvious for at least the following reasons. First, although Anderson allegedly tackles the problem of incompatible or wasteful reagents in a batch synthesis process, there is no reason why one of skilled in the art would combine a batch synthesis reactor with a completely different synthesis apparatus directed to pulse-jetting an addressable array, as taught by Bass. Second, the combination of the cited references would, at best, only lead one of skilled in the art to enclose Bass’s substrate in a centrifugal rotor and such an attempt to modify the teachings of the cited references to comport with the rejected claims would either render the combination inoperable or change the original principle of operations. Lastly, considering the art around the priority date of the instant application, it is apparent that the prevalent teaching involves methods that do **not** displace “a previous liquid [...] with an immediately subsequent liquid.” As such, the rejected claims are not obvious and this rejection should be withdrawn.

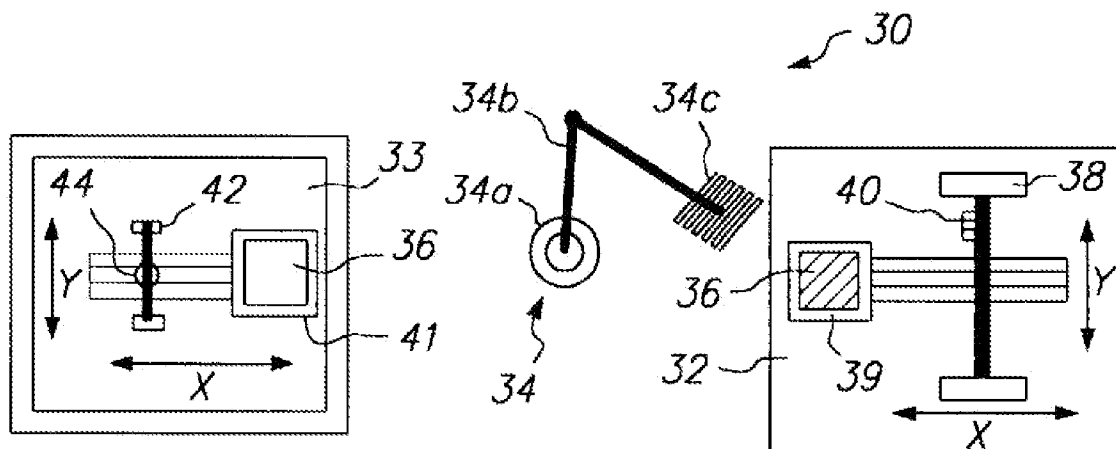
***Rejections - 35 USC § 103 Bass ‘669 and Anderson***

Claims 1, 3-7, 9-11, 14-16, 28, and 34-37 are rejected under 35 U.S.C. 103(a) as being obvious over Bass et al. (USPN 6,440,669) in view of Anderson et al. (USPN 5,186,824). The Applicants traverse this rejection.

As noted above, a *prima facie* case of obviousness requires the Office to articulate, *inter alia*, a reason for combining the elements.

In making this rejection, the Examiner reiterates the same reason here that one of skilled in the art would combine the cited references in a manner to comport with the rejected claims because Anderson teaches the problems of incompatible reagents. The Applicants submit for the same reasons discussed in the previous rejection, that combination of Bass '669 and Anderson would not lead one of skilled in the art to arrive at the rejected claims.

Similarly to Bass '180, Bass '669 teaches an addressable array made by contact printing using an inkjet deposition apparatus. The synthesis taught by Bass '669 involves an apparatus where an array substrate is moved from one platform to another, such that deposition of phosphoramidite happens in the first platform **32** and the array is transferred to the second platform **33** for oxidation, washing and drying (columns 15-16). The apparatus of Bass '669 as illustrated in Fig. 2 is reproduced below.



Bass '669 explains the washing steps in detail in column 16, lines 24-35, where “prior to contact with a wash liquid, wafer **36** may be treated to remove excess and unreacted reagents.” Bass continues on to say “such treatment may be by spinning, suction or vacuum, contact with an inert gas [....]”

In view of such teaching from Bass '669, Bass is completely silent on “displacing a previous liquid [...] with an immediately subsequent liquid.” In an attempt to remedy the deficiency of Bass '669, the Examiner cites Anderson.

As explained above, Anderson teaches a rotating rotor to synthesize batch oligonucleotides on CPG beads. Similar to the combination of Bass '180 and

Anderson, combining Bass '669 with Anderson as suggested by the Examiner would either change the principle of operation of the methods taught by the references or render them inoperable. Under current law, such logic cannot be used to establish a *prima facie* case of obviousness.

Briefly, the proposed modification would result in an embodiment where the substrate of the addressable array may be damaged while experiencing centrifugal force inside Anderson's rotor. Since a glass bead is not an addressable array nor can Bass's substrate exist in suspension, it would render either Bass's method or Anderson's method inoperable.

Furthermore, the proposed modification would change the principle of operation of the cited references. A mounted substrate in Anderson's rotor would not contain the element of suspended solid-phase in a rotating chamber taught by Anderson. As for Bass '669, Bass's method comprises moving the substrate between two stations, where one station involves drying steps during washing steps (columns 15 and 16). If Bass were to be combined with Anderson's method, the two station system would be completely eliminated since Anderson's rotor cannot accommodate two stations where the array substrate moves to and fro. In addition, the steps of drying the substrate would have to be eliminated as well since there is nothing in Anderson's rotor for drying an enclosed array substrate. A *prima facie* case of obviousness cannot be established by completely eliminating the principle operation of Bass or Anderson.

Moreover, as discussed previously, a consideration of the field of array synthesis reveals that much of the teaching around the priority date of the instant application comprises drying steps in between wash steps and is completely devoid of the element on "displacing a previous liquid [...] with an immediately subsequent liquid." Added to the list of patents discussed in the previous rejection is a cited patent in this rejection: Bass '669. Even Bass '669 teaches getting rid of "excess reagents by vacuum, suction, or inert gas" (Column 16, lines 30-32).

Given the popular teachings in the art of array synthesis that employ air drying and that are completely silent on "displacing a previous liquid [...] with an immediately subsequent liquid," one of skilled in the art would not have any reason to combine Bass '669 and Anderson in the manner suggested by the Examiner without the hindsight provided by the Applicants' application.

In view of the foregoing discussion, the Applicants submit for the following reasons why the claims cannot be rendered obvious by Bass '669 and Anderson. First, although Anderson allegedly tackles the problem of incompatible or wasteful reagents in a batch synthesis process, there is no reason why one of skilled in the art would combine a batch synthesis reactor with a completely different method directed to pulse-jetting an addressable array, as taught by Bass. Second, the combination of the cited references would, at best, only lead one of skilled in the art to enclose Bass's substrate in a centrifugal rotor and such an attempt to modify the teachings of the cited references to comport with the rejected claims would either render the combination inoperable or change the original principle of operations. As such, Bass alone or in combination with Anderson cannot render the rejected claims obvious. Lastly, considering the art around the priority date of the instant application, including Bass '669, it is apparent that the prevalent teaching involves methods that do **not** displace "a previous liquid [...] with an immediately subsequent liquid."

The Applicants contend that all claim rejections should be withdrawn based on the reasons set forth above. However, the Applicants further note that the combination of the cited references also does not teach or suggest the following dependent claims.

With respect to Claim 10, the Applicants submit that neither Bass '669 nor Anderson teaches or suggests that the "plurality of liquids are flowed [...] at a rate ranging from about 1 cm/s to about 20 cm/s." In making this rejection, the Examiner asserts that Anderson in columns 5, 14, and 21, teaches that "flow rate is adjusted to maximize reagents and synthetic step (page 11 of Final Office Action dated 8/12/08), and as such, it would have been obvious to one of skilled in the art to obtain optimal flow rates.

However, a detailed examination of these passages cited by the Examiner fails to reveal anything in Anderson relating to optimal flow rate. In column 5, Anderson teaches a rotating processor to "facilitate precise control of fluid flow to minimize anomalous flow." In column 14, Anderson teaches a density sensor to see if the density of the solution is appropriate. Finally, in column 21, Anderson teaches that the reason to minimize flow reversals (column 21, lines 30-65) is to minimize reagent consumption because switching incoming flow from the lower seal to the upper seal or vice versa requires more excess flow.



In view of the above, it is apparent that nowhere in Anderson is there a teaching or suggestion relating to **flow rate**. The Examiner's assertion of flow rate adjusted to maximize reagents and synthetic step taught by Anderson is unsupported. As such, the Examiner fails to articulate any reasoning that would have prompted one of skilled in the art to arrive at the flow rate ranging "from about 1 cm/s to about 20 cm/s." Withdrawal of the rejection of Claim 10 is thus respectfully requested.

With respect to Claim 11, the Applicants contend that neither Bass nor Anderson teaches or suggests "sensing movement of the stratified fluid interface." As best understood by the Applicants, the Examiner seems to point to the same passages in Anderson as those for the rejection of Claim 10.

The Applicants submit that the cited passages, as discussed above, are not only deficient in teaching flow rates, but are also completely silent on "sensing movement of the stratified fluid interface." Since no teaching or suggestion is found anywhere in the cited references, rejection of Claim 11 should be withdrawn.

In view of the foregoing discussion, the combination of Bass '669 and Anderson cannot render the rejected claims obvious because among other reasons discussed previously, the combination would not lead one of skilled in the art to arrive at the rejected claims without the hindsight of the instant application. The Applicants further submit that dependent claims 10-11 are also nonobvious over Bass and Anderson for additional reasons discussed above. As such, the combination of these cited references fails to establish a *prima facie* case of obviousness and the Applicants request that the rejection be withdrawn.

#### ***Rejections - 35 USC § 103 Bass '669, Anderson, and Golberg***

Claims 29-33 have been rejected under 35 U.S.C. 103(a) as being obvious over Bass et al. (USPN 6,440,669) in view of Anderson et al. (USPN 5,186,824), in further view of Goldberg (USPN 5,959,098). The Applicants traverse this rejection.

In making this rejection, the Examiner acknowledges that Bass and Anderson do not teach "plane of the flow cell or environment" and cites Goldberg in an attempt to remedy the deficiency of Bass and Anderson.

As noted above, Bass and Anderson cannot be used to establish a *prima facie* case of obviousness because the combination of the two methods would either

render Bass's method or Anderson's method inoperable or change their principles of operation. Moreover, popular array synthesis methods around the time of filing are completely silent on "displacing a previous liquid [...] with an immediately subsequent liquid." Rather, the prevalent practice demonstrated by various patents resorts to air-drying. As such, there is no reason for one of skilled in the art to combine the elements from Bass and Anderson in the manner suggested by the Examiner without the hindsight provided by the Applicants.

Since Goldberg is cited solely for the alleged teaching of a flow cell in vertical alignment, Goldberg cannot remedy the deficiency of Bass and Anderson discussed above. As such, the Applicants respectfully request the withdrawal of this rejection.

**CONCLUSION**

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 327-3400.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10040506-1.

Respectfully submitted,

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